

REMARKS

In an Office Action dated February 28, 2006, pending claims 1-18 were rejected. This document is submitted in response to said Office Action.

Claim Objections

The Examiner has objected to claims 2, 8 and 14 due to informalities wherein the claims contain non-elected subject matter and grammatical structure. The claims have been amended herein to correct for the non-elected subject matter and structure. Claim 13 was objected to due to minor grammatical errors. Claim 13 has been amended herein to correct for this error.

Double Patenting

The Examiner has rejected claims 1-18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-14 of US Patent No. 6,713,616 and claims 2-4 of US Patent No. 6,346,611. The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to methods of using the compounds claimed in each of the patents. The Examiner reasons that the patentability of the patented claims is considered in view of the ability to make and use the compound, thus the uses of these compounds recited in the instant claims would have been obvious in view of the patentability of the compounds.

An obviousness-type double patenting rejection is appropriate when a claim merely defines an obvious variation of an invention claimed in a patent. M.P.E.P. § 804(II)(B)(1). A double-patenting rejection must rely on a comparison with the claims in an issued or to be issued patent. M.P.E.P. § 804(III).

Applicants submit that Claims 1-18, as amended, which are directed to a method for inhibiting a transforming growth factor $\beta 2$ (TGF $\beta 2$), a method for targeting a nucleic acid ligand of TGF $\beta 2$ to a site in a patient, and a method for treating TGF $\beta 2$ -mediated pathological conditions are not obvious variations of claims 9-14 of US Patent No. 6,713,616 and claims 2-4 of US Patent No. 6,346,611. Although the patentability of the patented claims is considered in view of the ability to make and use the compound under 35 U.S.C. § 101, the comparison in an

obviousness-type double patenting rejection is appropriate between the issued claims, and whether or not what is claimed in the application is an obvious variation of what was claimed in the issued patent. In the present case, it is not obvious that producing the compounds claimed in claims 9-14 of US Patent No. 6,713,616 and claims 2-4 of US Patent No. 6,346,611, will provide for a method for inhibiting a transforming growth factor $\beta 2$ (TGF $\beta 2$), a method for targeting a nucleic acid ligand of TGF $\beta 2$ to a site in a patient, and a method for treating TGF $\beta 2$ -mediated pathological conditions. These methods are specifically claimed because a ligand to TGF $\beta 2$ may have many uses. Reconsideration is respectfully requested.

Claim Rejections under 35 USC §112—Written Description Requirement

The Examiner has rejected claims 1-18 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-6 are directed to methods of inhibiting a TGF $\beta 2$ by contacting the TGF $\beta 2$ with a nucleic acid ligand of TGF $\beta 2$. The Examiner asserts that the specification does not describe the full genus of nucleic acid ligands to human TGF $\beta 2$ by describing the structural features shared by the disclosed nucleic acid ligands that provide the function of inhibiting human TGF $\beta 2$ and does not disclose the structure of any nucleic acid ligands that function to inhibit TGF $\beta 2$ from any species other than human.

The Guidelines for Examination of Patent Applications under the 35 USC 112, 1, "Written Description" Requirement, MPEP § 2163 II.A.3(a) (hereinafter, "Written Description Guidelines") state

Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the invention. Disclosure of any combination of such identifying characteristics that

distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient [citing *Eli Lilly*, 43 USPQ2d at 1406]. Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and function of the invention [citation omitted].

The level of skill and knowledge in the relevant art, as reflected by patents and printed publications, indicate that the art is mature. This is evidenced by the fact that at the time the application was filed, there were over 70 issued patents in the United States alone with the phrase "nucleic acid ligand" or "SELEX" in their abstracts (using the USPTO's Full-Text database). This includes patents directed to complexes of nucleic acid ligands with non-immunogenic high molecular weight compounds or lipophilic compounds (see page 13, lines 13-29 of the instant specification). Thus, this is a mature technology where the level of skill is high and advanced. In technologies which are mature, and where the knowledge and level of skill in the art is high, the Written Description Guidelines provide (see above) that a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention. In the present case, therefore, even if the specification disclosed only the SELEX method and methods for complexing nucleic acid ligands with non-immunogenic, high molecular compounds or lipophilic compounds, a written description rejection should not be made. The present specification discloses even more than a method and function, however. The present invention discloses numerous nucleic acid ligands to TGF β 2, and further discloses a specific complex of a TGF β 2 ligand and a polyethylene glycol. The present disclosure yields a high level of skill and knowledge in the art, representative primary amino acid structures, functional characteristics and the method of making the invention—all illustrating that the applicant was in possession of the invention at the time of filing of the application.

Additionally, according to the Written Description Guidelines, *MPEP* § 2163 II.A.3(a), the "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces."

Applicants are in possession of the genus of complexes of TGF β 2 nucleic acid ligands because the SELEX method was well known and advanced, because non-immunogenic high molecular weight compounds and lipophilic compounds were well known, and because methods for attaching such compounds to nucleic acids were well known. of about 80% between mammalian TGF β 2s. The process to obtain nucleic acid ligands to TGF β 2 involves the SELEX process, wherein the nucleic acid ligand can be selected for any mammalian TGF β 2. Given the high degree of sequence similarity between the TGF β 2s in mammals, Applicants submit that the written description requirement for nucleic acid ligands of TGF β 2 has been met.

The Examiner states that claims 7-12 are directed to methods of targeting a nucleic acid ligand to a site in a patient comprising TGF β 2 by covalently linking the nucleic acid ligand to either a non-immunogenic, high molecular weight compound or a lipophilic compound and administering the complex to a patient comprising TGF β 2. The Examiner argues that although the patient comprises TGF β 2, the method encompasses the targeting of nucleic acid ligands that are not directed to TGF β 2 to any site within the patient. The Examiner further argues that the method is directed to targeting nucleic acid ligands to a patient of any species that comprises TGF β 2. The Examiner further asserts that the claim recites conjugation of a nucleic acid ligand with a non-immunogenic high molecular weight compound or a lipophilic compound as necessary for targeting the nucleic acid ligand to a site within a patient, but the specification does not describe a representative sample of sites within a patient that can be targeted by administration of such conjugates.

Applicants have amended claim 7 to further clarify that the nucleic acid ligand itself is targeted to TGF β 2. Applicants point out that the coupling of the nucleic acid ligand to either a non-immunogenic, high molecular weight compound or a lipophilic compound is not necessary for specifically targeting the nucleic acid ligand to the TGF β 2. The nucleic acid ligand is targeted to the TGF β 2 based on the affinity of the ligand to its target, and therefore targeting to the TGF β 2 is accomplished by the nucleic acid ligand, not the non-immunogenic, high molecular

weight compound or lipophilic compound. The targeting of the nucleic acid ligand is to TGF β 2; therefore, the site of targeting is to wherever the TGF β 2 is located in the patient. The method does not encompass the targeting of nucleic acid ligands that are not directed to TGF β 2 to any site within the patient, because the targeting is a functional property of any nucleic acid ligand of TGF β 2.

The Examiner continues by stating that claims 13-18 are directed to methods of treating a TGF β 2-mediated pathological condition by administering a nucleic acid ligand capable of binding to TGF β 2 to a patient in need thereof. The Examiner then asserts that neither the specification nor the prior art describes the full genus of pathological disorders that are mediated by TGF β 2, particularly in view of the teachings that TGF β 2 can both increase and decrease cellular proliferation and that TGF β 2 may be involved in autoimmune disorders and infectious diseases. The Examiner further argues that the specification does not describe the structure of any nucleic acid ligands that have the function of treating any TGF β 2-mediated pathological conditions in any species.

Although not every pathological disorder that is TGF β 2-mediated has been formally named as yet, the claims define the disorder as TGF β 2-mediated, which is specific to a class of pathological conditions and would be understood by one of skill in the art. Applicants have disclosed the structure of nucleic acid ligands that bind and inhibit the function of TGF β 2. One of skill in the art would additionally recognize that a pathological condition mediated by TGF β 2, could be treated by an inhibitor of TGF β 2.

For the foregoing reasons, Applicants respectfully submit that the specification meets the written description requirement of Section 112, and request that the rejection be withdrawn.

The Rejection under 35 U.S.C. § 112, first paragraph—Enablement Requirement

The Examiner has rejected claims 1-18 under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements

contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A. 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The Examiner asserts that while the specification is enabling for the use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells, the specification does not reasonably provide enablement for targeting a nucleic acid ligand to a site in a patient, inhibiting TGFβ2 *in vivo* or treating a pathological condition mediated by TGFβ2 *in vivo* in any organism using a nucleic acid ligand to TGFβ2.

The Examiner acknowledges that the specification is enabling for the use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells. However, the specification provides additional teachings relevant to this rejection. The specification discloses the pharmacokinetics of representative nucleic acid ligands to TGFβ2 in rats (see example 5, page 52). The specification also discloses isolation of nucleic acid ligands that bind human TGFβ2 (see example 2, page 31). Therapeutic compositions of the nucleic acid ligands are disclosed on page 19 lines 20-30. To provide guidance for *in vivo* stability of the nucleic acid ligands, the specification discloses various post-SELEX modifications (page 19, lines 1-12).

The Examiner cites Opalinska as evidence of the unpredictability in the art. However, Opalinska is referring to therapeutic uses of nucleic acids as opposed to the present invention of therapeutic uses of nucleic acid ligands. The difficulty described in Opalinska involves targeting a nucleic acid to genomic DNA, in a way that could facilitate hybridization. The present invention does not involve hybridizing nucleic acids to genomic DNA. The present use has been likened to antibody therapy, in that the nucleic acid ligands target a particular moiety.

Given the substantial disclosures as described above, in view of the standards imposed by Marzocchi and Wands, referenced above, Applicants submit that the enablement requirement for targeting a nucleic acid to a site in a patient, inhibiting TGFβ2 *in vivo* or treating a pathological

condition mediated by TGF β 2 *in vivo* using a nucleic acid ligand to TGF β 2 has been met.
Reconsideration is respectfully requested.


Closing Remarks

Applicants believe that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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